## REMARKS

Upon entry of the presently made amendments, claims 1-3, 7 and 9-19 will be pending. Claims 4-6 and 8 have been canceled without prejudice.

Claims 1, 9, 16 and 19 have been amended to recite groups that can be substituents. Support for these amendments is found in the specification as filed at least at page 9, line 21 to page 10, line 7.

Claims 1, 9, 16 and 19 have been further amended to recite a more focused class of compounds. Support for these amendments is found in the specification as filed at least at page 25, lines 8-11 and page 21, line 20 to page 23, line 6.

Claims 1, 9 and 19 have been further amended to recite that the disease or cancer to be treated or cancer cell to be inhibited is associated with a nonsense mutation in the p53 gene. Support for these amendments is found in the specification as filed at least at page 6, lines 27-29.

Claims 1, 9 and 16 have been further amended to recite methods of treatment. Support for these amendments is found in the specification as filed at least at page 7, lines 26-27.

No new matter has been added.

Applicants reserve their right to prosecute the subject matter of any canceled or amended claim or any unclaimed subject matter in one or more divisional, continuation or continuation-in-part applications.

### I. The Rejection of Claims 1-6 and 9-19 Under 35 U.S.C. § 112, Second Paragraph

Claims 1-6 and 9-19 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. In particular, the Examiner has stated that these claims are indefinite because the substituents of substituted groups are not defined. Without acquiescing in the rejection and solely to expedite prosecution, Applicants have amended claims 1, 9, 16 and 19 to recite particular groups that can be substituents.

Accordingly, Applicants respectfully submit that the amended claims satisfy the requirements set forth in 35 U.S.C. § 112, second paragraph, and that the rejection of claims 1-6 and 9-19 as being indefinite should be withdrawn.

## II. The Rejection of Claims 1-6 and 9-19 Under 35 U.S.C. § 112, First Paragraph

Claims 1-6 and 9-19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

While acknowledging that the specification is enabling for a method comprising administering the species recited in claim 7, the Examiner has stated that the specification does not reasonably provide enablement for a method comprising administering any compound of formula I.

Without acquiescing in this rejection and solely to expedite prosecution of the present application, Applicants have amended claims 1, 9, 16 and 19 to recite a more focused class of compounds. Applicants respectfully submit that the amended claims are reasonably enabled at least by the *in vitro* and *in vivo* nonsense mutation suppression data in connection with clitocine set forth in Examples 5.2.7-5.2.11 and the *in vitro* data in connection with additional compounds that are representative of this class set forth in Table 1 of the specification as filed.

Accordingly, Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-6 and 9-19 for lack of enablement has been overcome and should be withdrawn.

## III. The Rejection of Claims 1-3, 6, 9-11 and 18-19 Under 35 U.S.C. § 103(a)

Claims 1-3, 6, 9-11 and 18-19 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Sanghvi *et al.*, 1989, *J. Med. Chem. 32*:629-637 ("Sanghvi"). In particular, the Examiner has stated that Sanghvi discloses certain compounds that fall with the limits of the generic structure (I) in instant claim 1 and that the compounds are said to possess antitumor properties. Applicants respectfully traverse this rejection.

As discussed above, claims 1, 9 and 19 have been amended to recite a more focused class of compounds. In particular, the compounds are those wherein the variable Z is an optionally substituted pyrimidine, pyridine or phenyl group. In contrast, the compounds of Sanghvi contain a pyrimido[5,4-d]pyrimidine group.

Applicants respectfully submit that Sanghvi does not provide the requisite suggestion or motivation to modify the compounds described therein to arrive at the compounds of the amended method of use claims. *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991); *In re Grabiak*, 769 F.2d 729, 732 (Fed. Cir. 1985).

Accordingly, Applicants respectfully submit that the rejection of claims 1-3, 6, 9-11 and 18 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

## IV. The Rejection of Claims 1-15 and Under 35 U.S.C. § 112, First Paragraph

Claims 1-15 and 19 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

While acknowledging that the specification is enabling for the treatment of certain specific p53-associated tumors, the Examiner has stated that the specification does not reasonably provide enablement for the treatment of every type of cancer in existence.

Without acquiescing in this rejection and solely to expedite prosecution of the present application, Applicants have amended claims 1, 9 and 19 to recite that the disease or cancer to be treated or cancer cell to be inhibited is associated with a nonsense mutation in the p53 gene. Applicants respectfully submit that amended claims 1, 9, 19 and claims that depend therefrom, which are directed to more focused methods comprising the administration of a more focused class of compounds, are reasonably enabled at least by the data set forth in connection with clitocine and p53 in Examples 5.2.7-5.2.11 and the *in vitro* nonsense mutation suppression data in connection with additional compounds set forth in Table 1.

Accordingly, Applicants respectfully submit that the pending claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-15 and 19 for lack of enablement has been overcome and should be withdrawn.

## V. The Rejection of Claims 1-18 Under 35 U.S.C. § 112, First Paragraph

Claims 1-18 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

Applicants disagree with the Examiner's reasoning and respectfully submit that because compounds in the pending method of use claims are, without being limited by theory, believed to derive their therapeutic activity from their ability to suppress nonsense mutations, and such nonsense mutations are genetic mutations for which a patient can be screened, one skilled in the art could practice the claimed invention to prevent diseases associated with a nonsense mutation.

However, without acquiescing in the rejection and solely to expedite prosecution of the present application, claims 1, 9 and 16 have been amended to recite methods of treatment. Applicants acknowledge the Examiner's indication that the practice of administering a

therapy to a patient at risk for a disorder in order to reduce the likelihood or severity of the disorder is considered to be within the definition of the term "treatment."

In view of the above discussion and amendments to the claims, Applicants respectfully submit that the amended claims satisfy the enablement requirement set forth in 35 U.S.C. § 112, first paragraph, and that the rejection of claims 1-18 for lack of enablement should be withdrawn.

## VI. The Rejection of Claims 1-19 Under 35 U.S.C. § 103(a)

Claims 1-19 are rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over U.S. Patent No. 5,324,731 to Kaddurah-Daouk *et al.* ("Kaddurah-Daouk"). Applicants respectfully traverse this rejection.

As noted by the Examiner, Kaddurah-Daouk discloses methods of inhibiting the growth, transformation and/or metastasis of mammalian cells in which activity of at least one purine metabolic enzyme is elevated. Indeed, the entire focus of Kaddurah-Daouk is the use of certain compounds as inhibitors of purine metabolic enzyme activity, message level, expression or interaction with other viral or cell products (*see* Kaddurah-Daouk, col. 2, line 64 to col. 3, line 11). In other words, Kaddurah-Daouk only teaches the use of certain compounds to decrease enzyme activity. There is no discussion or suggestion in Kaddurah-Daouk of the use of any compound to suppress a nonsense mutation to promote the expression of a gene product.

Applicants respectfully disagree with the Examiner's reasoning that one of ordinary skill in the art would find it obvious from the disclosure of Kaddurah-Daouk to treat a cancer associated with a loss of p53 with any compound, let alone clitocine. Rather, the key marker that Kaddurah-Daouk points to is purine metabolic enzyme activity. Thus, regardless of the status of p53 in a patient's cells, if elevated purine metabolic enzyme activity is not detected, there would be no motivation to administer any compound of Kaddurah-Daouk. In other words, if it was determined that tumor cells from a patient were not characterized by elevated activity of a purine metabolic enzyme, there would be no motivation to administer clitocine, or any compound of Kaddurah-Daouk, regardless of the level of p53 expression. *In re Vaeck* at 493. In addition, there would be no expectation of success with respect to the treatment of such a disease which was not shown to be characterized by elevated activity of a purine metabolic enzyme. *Id.*

Furthermore, the Examiner has stated that the teaching of Kaddurah-Daouk that certain compounds which are inhibitors of a purine metabolic enzyme (*i.e.*, creatine kinase) lack anti-tumor activity does not provide a reason to doubt that the recited compounds,

including clitocine, are functional embodiments. Applicants respectfully disagree. Kaddurah-Daouk teaches that the compounds described therein have anti-tumor activity because of their ability to inhibit the activity of a purine metabolic enzyme, such as creatine kinase. Thus, Applicants respectfully submit that a showing that certain creatine kinase inhibitors lack anti-tumor activity does indeed provide a reason to doubt that other kinase inhibitors possess anti-tumor activity and, in fact, teaches away from their use as anti-tumor agents.

For these reasons, Applicants respectfully submit that the pending claims are not obvious over Kaddurah-Daouk.

Accordingly, Applicants respectfully submit that the rejection of claims 1-19 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

## VI. The Provisional Double Patenting Rejection

Claims 1-19 are provisionally rejected under the judicially created doctrine of double patenting over claims 1-10 of co-pending Application No. 11/048,659 (the "'659 application). Per M.P.E.P § 804, a provisional double patenting rejection should continue to be made unless it is the sole remaining rejection in one of the applications. Upon entry of the presently made amendment and remarks, Applicants believe that the sole remaining rejection in the present application will be the provisional double patenting rejection over the '659 application. Accordingly, Applicants respectfully request that the provisional double patenting rejection over the '659 application be withdrawn. Applicants will then consider filing a terminal disclaimer in the '659 application over the present application.

## Conclusion

Applicants respectfully request that the above amendments and remarks be entered in the present application file. No fee is believed to be due in connection with this Response other than that in connection with the Petition for Extension of Time; however, in the event that any additional fee is due, please charge the required fee to Jones Day Deposit Account No. 50-3013.

Respectfully submitted,

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Enclosures